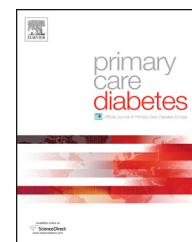




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Review

IDegLira: Redefining insulin optimisation using a single injection in patients with type 2 diabetes



Eugene Hughes*

The Esplanade Surgery, 19 The Esplanade, Ryde PO33 2EH, Isle of Wight, UK

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ABSTRACT

In type 2 diabetes (T2D), treatment is optimised to minimise hyperglycaemia and the risk of microvascular complications. While there are a number of effective treatments, intensive treatment is associated with negative side effects such as increased hypoglycaemia and weight gain.

With complementary modes of action, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and a basal insulin in combination offer an alternative to basal-bolus therapy in T2D. This review describes the rationale behind this treatment combination and presents clinical data available for IDegLira, the first basal insulin (insulin degludec) and GLP-1RA (liraglutide) co-formulation available in one pen for a single injection daily.

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* Tel.: +44 01983 618388; fax: +44 01983 618398.

E-mail address: eugenejhughes@gmail.com

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1. The need for treatment optimisation

The natural progression of type 2 diabetes (T2D), from impaired glucose tolerance through to overt T2D, is characterised by increasing insulin resistance and decreased endogenous insulin production [1]. As deterioration in beta-cell function continues beyond diagnosis, effective management of T2D typically requires therapy to be monitored and periodically intensified to prevent worsening blood glucose control [2,3]. As such, current treatment guidelines recommend a stepwise approach to T2D therapy, with the addition of second- and third-line antidiabetic agents if glycaemic targets are not met within 3 months. This involves regular monitoring of the patient's blood glucose with progression to daily self-measuring if the patient is prescribed insulin [1,4,5].

Chronic hyperglycaemia and poor glycaemic control increase the risk of patients with T2D developing microvascular complications such as retinopathy, neuropathy and nephropathy [2,6,7]. In contrast, it is widely accepted that improvements in glycaemic control and intensive therapy aimed at reaching strict glycaemic targets can reduce the risk of such microvascular complications developing and progressing [2,6].

Unfortunately, despite the current guidelines, many patients with T2D are still failing to meet glycaemic targets. In the UK, more than two-thirds (73.8%) of patients with T2D are failing to meet the NICE-recommended intensive glycaemic control target of $HbA_{1c} < 6.5\%$ [8]. This is the case even for those patients receiving insulin therapy, with more than half of patients with T2D on basal insulin not achieving good glycaemic control [9–11]. While intensive treatment has demonstrated significant benefits in T2D, treatment intensification – particularly with insulin therapy – is associated with weight gain [2,12,13], an increase in the incidence of hypoglycaemia [14] and a higher rate of severe hypoglycaemia [2,12,15]. There is, therefore, resistance among both patients and physicians to intensifying insulin therapy, with many patients fearful of the increased risks of hypoglycaemia and weight gain [16].

2. Current treatment options

The aim of treatment in T2D is to maintain good glycaemic control (and thus reduce the risk of micro- and macrovascular complications) while at the same time reducing the risk of adverse effects of therapy such as hypoglycaemia and weight gain [4]. In recent treatment guidelines, there has also been an increasing focus on individualising both therapy and goals in T2D to best address patient needs [1]. For example, while recommending an overall HbA_{1c} target of 6.5%, current NICE guidelines for the management of T2D also emphasise the need for individualised, patient-centred care and involving patients in their care decisions (e.g. HbA_{1c} target setting) [4]. As part of this, there have also been calls to consider earlier initiation of both glucagon-like peptide-1 receptor agonists (GLP-1RAs) and basal insulin therapy in the treatment pathway [1], with the hope that this might slow disease progression and preserve some pancreatic function in some patients.

As is evident in the current NICE clinical care pathway for T2D (Fig. 1) [1], while there is a wide range of treatment options and a number of factors to take into account, treatment usually follows a standard pattern of optimisation and intensification (Fig. 1) [1]. The first line of treatment after diagnosis is predominantly diet and lifestyle modification, although some may favour initiation of metformin at diagnosis depending on the patient and their level of hyperglycaemia. Treatment progression then usually proceeds with the subsequent inclusion of additional oral antidiabetic drugs (OADs), such as sulphonylureas or dipeptidyl peptidase-4 (DPP-4) inhibitors, or GLP-1RAs as indicated when failure to control HbA_{1c} with metformin alone occurs [1,4]. After failure of glycaemic control on two or more OADs (including metformin), patients will generally be initiated on basal insulin in order to reach the agreed-upon glycaemic targets. Further optimisation may include the addition of 1–3 bolus doses of prandial insulin or additional basal insulin doses, although there has been some suggestion that the use of twice-daily premixed insulin may be preferable to basal-bolus treatment regimens in T2D [17].

While the use of basal insulin is well established as effective in T2D, insulin therapy has traditionally been seen as a treatment of last resort and there is evidence that physicians delay both initiation and intensification of insulin, even when glycaemic control is poor [16,18]. Nevertheless, various studies have investigated the effects of adding multiple bolus insulin doses in various regimens in patients with insufficient glycaemic control on basal insulin alone [19–22]. These studies have demonstrated significant glycaemic benefits in T2D with the addition of either a single bolus dose of insulin to basal insulin and OADs [19] or the addition of multiple doses of bolus insulin in either full basal-bolus or stepwise manner [20–22]. Results from these studies show that, while there is still discussion over how best to intensify insulin therapy, such treatment is effective in T2D.

Unfortunately, the HbA_{1c} reduction achieved with treatment intensification is often accompanied by weight gain, an increased risk of hypoglycaemia and the requirement to administer and adjust additional daily insulin injections [2,12–14,23]. Fear of these side effects can lead to both patients and physicians delaying initiation of insulin and, once initiated, increasing insulin dose or adding additional injections [16].

Because of these issues, several published studies have investigated the feasibility of combining GLP-1RAs with basal insulin as an alternative to basal-bolus insulin therapy in T2D [24–26]. There is also some evidence that the use of these drug classes together is becoming more common in the clinic, particularly with the addition of liraglutide to basal insulin [27]. Nevertheless, this approach still requires multiple daily injections and is subject to the gastrointestinal-related side effects associated with the initiation and up-titration of GLP-1RAs. However, a fixed-ratio combination of these agents, with slow titration, has the potential to address both fasting and postprandial control without incurring the tolerability issues associated with prandial insulins and the gastrointestinal-related side effects of GLP-1RAs [24–26]; hence there is a rationale for developing such a combination product.

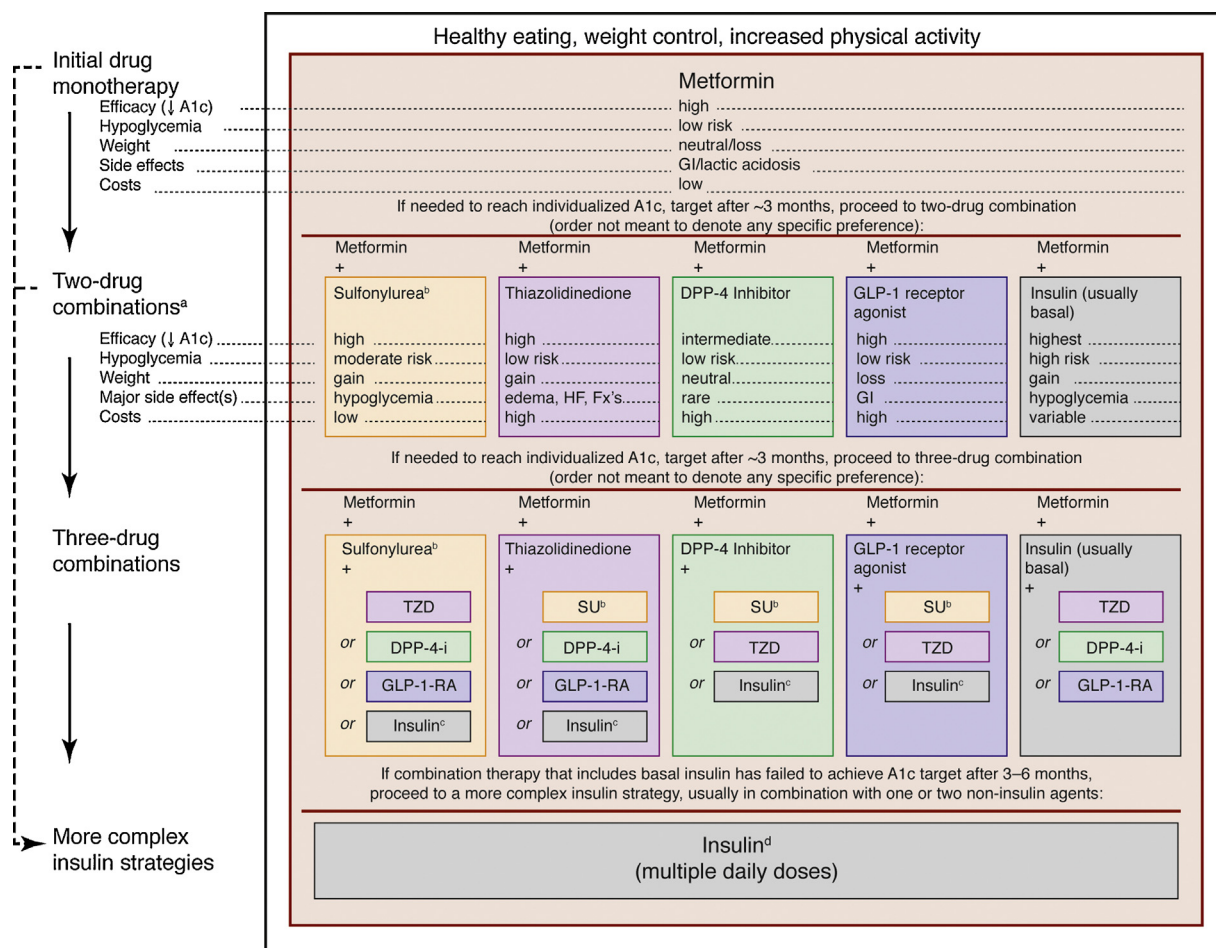


Fig. 1 – Care pathway for treatment of type 2 diabetes [1]. A1c, glycated haemoglobin (HbA_{1c}); DPP-4i, dipeptidyl peptidase-4 inhibitor; Fx, bone fracture; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SU, sulphonylurea; TZD, thiazolidinedione. Reproduced with kind permission from Springer Science+Business Media: *Diabetologia* 55 (2012) 1577–1596.

3. Combining basal insulin and GLP-1RA effects: IDegLira

The GLP-1RA component of IDegLira, liraglutide, is a once-daily human GLP-1 receptor agonist (GLP-1RA) that shares a 97% amino acid sequence identity with human GLP-1 [28,29]. The efficacy and safety of liraglutide has been demonstrated via the LEAD phase 3 clinical trial programme, which included a total of 4456 subjects, 2739 of whom were treated with liraglutide [30–36]. A meta-analysis of the phase 3 data has shown a mean reduction in HbA_{1c} of 1.5% with liraglutide 1.8mg and 1.3% with liraglutide 1.2mg when added to unchanged background treatment (vs. 0.3% with placebo, $p < 0.0001$) [37]. As with other GLP-1RAs, liraglutide also shows benefits regarding body weight in T2D with significantly greater loss with liraglutide than placebo or active comparators [38].

The insulin component of IDegLira, insulin degludec, is a long-acting basal insulin analogue with a half-life twice as long as that of insulin glargine and low day-to-day variability in glucose-lowering effect [39,40]. The efficacy of insulin

degludec in T2D as part of both basal-bolus therapy and basal-only therapy has been assessed as part of the BEGIN phase 3 clinical trial programme [41–44]. In insulin-naïve patients with T2D, insulin degludec has demonstrated comparable glycaemic control to insulin glargine when titrated to a common blood glucose target but with a significantly lower rate of nocturnal hypoglycaemia (43% lower than with glargine, $p = 0.002$) after 2 years of treatment [44]. As part of a basal-bolus regimen in T2D, insulin degludec was shown to provide comparable glycaemic control to insulin glargine but with an 18% lower rate of overall hypoglycaemia ($p = 0.0359$) and a 25% lower rate of nocturnal hypoglycaemia ($p = 0.0399$) over 52 weeks of treatment [41].

The concept of treating T2D with basal insulin and a GLP-1RA in combination is particularly appealing as the two drug classes address different aspects of the pathophysiological deficits in T2D. Separately, each can safely and effectively help many patients achieve recommended glucose targets when they are no longer able to do so with lifestyle modification and OADs alone [23,45]. Together, they may have complementary actions, with basal insulin providing a reduction in fasting blood glucose while the GLP-1RA ameliorates

postprandial excursions due to the glucose-dependent mechanism of action.

Given this potential for complementary glucose-lowering effects, the addition of liraglutide to basal insulin (insulin degludec) therapy has already been explored in T2D [24]. In a study in patients inadequately controlled on basal insulin and metformin, the addition of liraglutide (1.2 mg increased to 1.8 mg if fasting plasma glucose [FPG] ≥ 5.0 mmol/L at week 5) was compared with the addition of a single bolus dose of insulin aspart [24]. The results showed a greater reduction in HbA_{1c} with liraglutide than aspart (-0.74% vs. -0.39% , $p < 0.001$), with lower rates of hypoglycaemia and a weight loss of 2.8 kg versus weight gain with insulin aspart [24].

While several such combination products are currently in development or clinical trials, IDegLira is the first combination of a basal insulin analogue (degludec) and a GLP-1RA (liraglutide) in single daily injection to be approved for use in Europe. IDegLira is administered via a pre-filled pen with a fixed ratio of insulin degludec (100 U/mL) and liraglutide (3.6 mg/mL). IDegLira uses a simplified titration algorithm based on dose steps, with each dose step consisting of one unit of insulin degludec and 0.036 mg liraglutide. The initial dose of IDegLira is 10 dose steps (10 units of insulin degludec and 0.36 mg liraglutide) in individuals uncontrolled on OADs and 16 dose steps (16 units of insulin degludec and 0.6 mg liraglutide) in those previously receiving basal insulin or a GLP-1RA. The dose is adjusted based on self-measured blood glucose targets and with a maximum dose, per injection once daily, of 50 units of insulin degludec and 1.8 mg liraglutide [46].

4. Comparison with individual components

To date, data have been published from two phase 3a clinical trials of IDegLira, one in insulin-naïve patients and one in patients previously treated with basal insulin.

The first of these (DUAL I) was a randomised, open-label study of IDegLira versus insulin degludec or liraglutide alone in

insulin-naïve patients previously treated with metformin with or without pioglitazone [47]. The main trial of 26 weeks was extended to a year to assess the durability of the treatment effect [48]. The starting dose for both IDegLira and insulin degludec was 10 dose steps/units and dose adjustments were made twice weekly (± 2 dose steps/units to an FPG target of 4.0–5.0 mmol/L). The starting dose for liraglutide was 0.6 mg with titration up to 1.8 mg by 0.6 mg per week, as per the label.

In the second study (DUAL II), a randomised, double-blind trial of IDegLira versus insulin degludec in patients previously receiving 20–40 units of basal insulin, the starting dose for both IDegLira and insulin degludec was 16 dose steps/units, again with dose adjustments made twice weekly (± 2 dose steps/units to an FPG target of 4.0–5.0 mmol/L). However, in this study, the maximum dose of insulin degludec in both the IDegLira and insulin degludec arms was capped at 50 dose units [49]. This was in order to specifically demonstrate the additional contributions of the liraglutide component of IDegLira.

In the results published to date, IDegLira has demonstrated several significant benefits over each of the individual components in both insulin-naïve patients [47] and in those previously treated with basal insulin [49] (summarised in Table 1). In insulin-naïve patients, IDegLira produced a significantly greater reduction in HbA_{1c} (-1.9%) than either degludec (-1.4%) or liraglutide (-1.3%) after 26 weeks' treatment ($p < 0.0001$ for both) (Fig. 2) [47,49].

Improvement in HbA_{1c} was accompanied by a mean body weight reduction of -0.5 kg with IDegLira, compared with a weight increase of 1.6 kg with degludec ($p < 0.0001$ vs. IDegLira) and a weight loss of 3.0 kg with liraglutide ($p < 0.0001$ vs. IDegLira). In addition, a significantly greater proportion of the IDegLira group reached glycaemic targets of HbA_{1c} $< 7.0\%$ (81% with IDegLira vs. 65% with insulin degludec and 60% with liraglutide, $p < 0.0001$) and $\leq 6.5\%$ (70% with IDegLira vs. 48% with insulin degludec and 41% with liraglutide, $p < 0.0001$).

The additional glucose-lowering effect provided by liraglutide in the combination also reduces the dose of insulin

Table 1 – Response to IDegLira in phase 3a and phase 3b clinical trials [47,49].

Citation	Trial name	Trial duration	Prior treatment	Comparator	Δ HbA _{1c} IDegLira vs. comparator, ETD (%)	Δ body weight IDegLira vs. comparator, ETD (kg)	Hypoglycaemia* events/PYE, IDegLira vs. comparator, ERR
Gough et al. [47]	DUAL I main trial	26 weeks	Metformin \pm pioglitazone	IDegLira vs. IDeg;	-1.9 vs. -1.4% , -0.47% [-0.58 ; -0.36] _{95% CI} , $p < 0.0001$;	-0.5 vs. 1.6 kg, -2.22 kg [-2.64 ; -1.80] _{95% CI} , $p < 0.0001$;	1.8 vs. 2.6, 0.68 [0.53; 0.87] _{95% CI} , $p = 0.0023$;
				IDegLira vs. liraglutide	-1.9 vs. -1.3 , -0.64% [-0.75 ; -0.53] _{95% CI} , $p < 0.0001$	-0.5 vs. -3.0 kg, 2.44 kg [2.02; 2.86] _{95% CI} , $p < 0.0001$	1.8 vs. 0.2, 7.61 [5.17; 11.21] _{95% CI} , $p < 0.0001$
Buse et al. [49]	DUAL II	26 weeks	Basal insulin + metformin \pm SU	IDeg (max. dose 50 U)	-1.9 vs. -0.9% , -1.1% [-1.3 ; -0.8] _{95% CI} , $p < 0.0001$	-2.7 vs. 0.0 kg, -2.5 kg [-3.2 ; -1.8] _{95% CI} , $p < 0.0001$	1.5 vs. 2.6, 0.66 [0.39; 1.13] _{95% CI} , $p = 0.13$

CI, confidence interval; ETD, estimated treatment difference; ERR, estimated rate ratio; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide; PYE, patient-year of exposure; SU, sulphonylurea.
* Severe, or plasma glucose < 56 mg/dL.

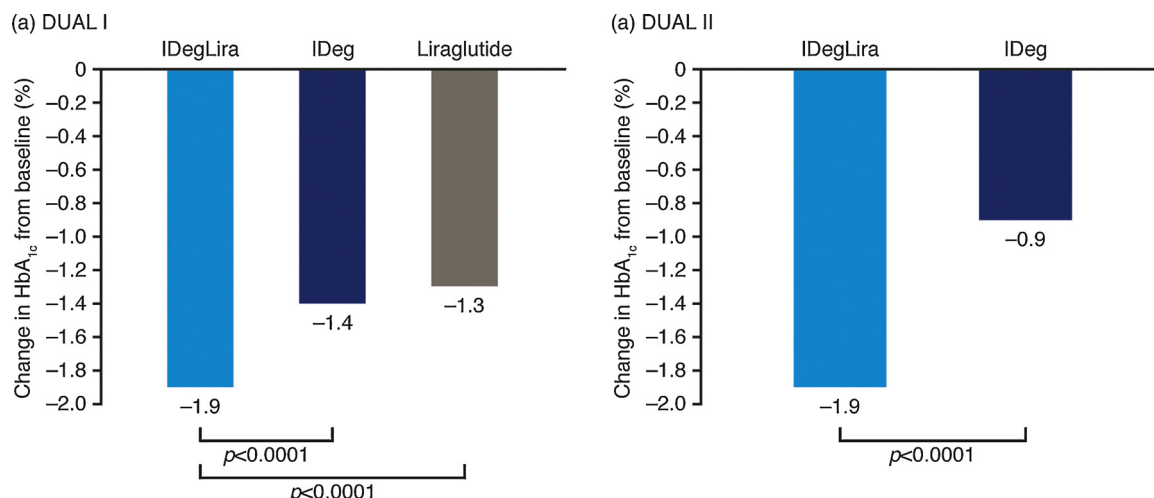


Fig. 2 – Change in HbA_{1c} from baseline with IDegLira and comparators in (a) insulin-naïve patients [47] and (b) patients previously treated with basal insulin [49]. IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide

required to reach the same glycaemic target. In DUAL I, the end-of-trial insulin dose was 28% lower with IDegLira than insulin degludec (38 vs. 53 units, $p < 0.0001$), despite the significantly greater reduction in H

bA_{1c} with IDegLira [47]. This reduced dose of the insulin component likely contributes to the significantly (32%, $p = 0.0023$) lower rate of hypoglycaemia seen with IDegLira than with degludec in this trial, despite the lower end-of-trial HbA_{1c} (6.4 vs. 6.9% [46 vs. 52 mmol/mol]). As would be expected, few subjects reported hypoglycaemia with liraglutide. Results of the DUAL I extension study showed that the efficacy and safety of IDegLira demonstrated in the main trial were maintained for a year [48].

Interestingly, in DUAL I, the proportion of patients experiencing nausea with IDegLira was significantly lower with IDegLira than with liraglutide over the full course of the main trial (Fig. 3) [47]. This is likely due to the slower titration of

liraglutide as part of the combination, where the increase in dose was based on titration of the degludec component compared with liraglutide, in which the standard liraglutide titration was followed. IDegLira is now approved in Europe for use in patients uncontrolled on GLP-1RA therapy and oral glucose-lowering products [46]; results from a phase 3b trial in which patients with T2D inadequately controlled on GLP-1RA therapy (maximum dose tolerated or locally approved) were randomised to either switch to IDegLira, with initiation at 16 dose steps, or to continue on unchanged GLP-1RA therapy, demonstrated that IDegLira was superior with respect to mean HbA_{1c} reduction in this population. The mean IDegLira dose after 26 weeks of treatment was 43 dose steps, which corresponds to 43 units of insulin degludec and 1.55 mg liraglutide [50].

In patients previously treated with basal insulin, IDegLira demonstrated significantly greater reduction in HbA_{1c} compared with insulin degludec after 26 weeks of treatment (−1.9% vs. −0.9%, $p < 0.0001$) (Fig. 2) [49]. In these patients, IDegLira produced a mean weight loss of 2.7 kg compared with no weight change with insulin degludec.

Rate of confirmed hypoglycaemia (including severe events and defined as plasma glucose < 3.1 mmol/L regardless of symptoms, or if required assistance) was comparable between the two groups (1.5 vs. 2.6 events/patient-year; $p =$ not significant) with similar incidences (IDegLira 24% vs. insulin degludec 25%) and a lower end-of-trial HbA_{1c} with IDegLira (6.9% vs. 8.0%) [49].

In both of these phase 3a studies, IDegLira demonstrated superior HbA_{1c} control to either of the components, basal insulin degludec or liraglutide, alone. IDegLira also demonstrated additional benefits of a single injection rather than multiple daily insulin doses and a decreased incidence of nausea (a common side effect of GLP-1RAs), and the weight gain that is a characteristic of treatment with basal insulin. These data suggest potential benefits of IDegLira in patients with insufficient glycaemic control but for whom weight loss and/or avoidance of an increased risk of hypoglycaemia is desirable.

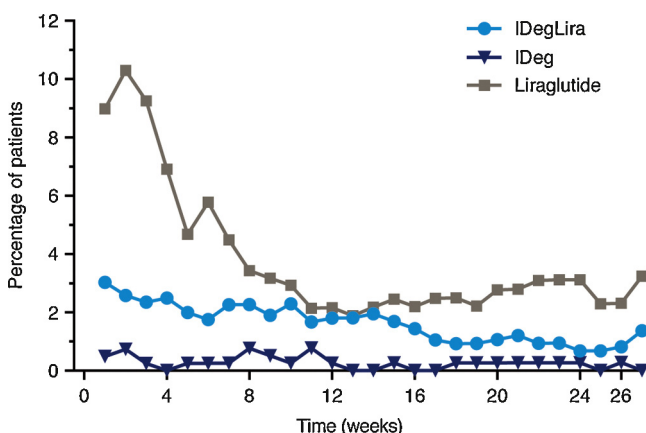


Fig. 3 – Proportion of patients experiencing nausea with IDegLira versus liraglutide in the DUAL I study [47]. IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide. Reprinted from Lancet Diabetes Endocrinol. 2 (2014) 885–893, with permission from Elsevier Ltd.

5. Clinical considerations

IDegLira is given once daily by subcutaneous administration. It can be given at any time of the day, preferably at the same time each day.

Dosing of IDegLira is done in 'dose steps' rather than units as each dose step contains one unit of insulin degludec and 0.036 mg of liraglutide. The titration algorithm will be based on the average of three morning blood glucose readings [46]. For patients who are adding IDegLira to existing OADs, the recommended starting dose is 10 dose steps. IDegLira can be added to existing OADs, but a reduction in the dose of sulphonylurea should be considered when added to sulphonylurea therapy. Any therapy with basal insulin should be discontinued prior to initiation of IDegLira, and when transferring from basal insulin therapy, the recommended starting dose of IDegLira is 16 dose steps [46]. Similarly, for patients currently uncontrolled with a GLP-1RA, existing GLP-1RA therapy should be discontinued prior to initiation of IDegLira at a starting dose of 16 dose steps. This corresponds to a starting dose of 0.6 mg, as recommended for patients beginning liraglutide treatment [51].

6. Conclusions

Due to the progressive nature of T2D, the majority of patients will require increasing intensification of treatment in order to maintain good glycaemic control and a large proportion of patients will eventually require insulin therapy. Unfortunately, while the initiation of insulin and intensification of insulin therapy with additional bolus doses has proven efficacy in T2D, it is associated with significant side effects such as weight gain and hypoglycaemia.

The combination of GLP-1RAs with basal insulin has been investigated in T2D populations in several clinical trials with positive results. IDegLira is the first basal insulin and GLP-1RA in one pen for a once-daily injection and offers a new treatment option for patients who require treatment optimisation.

Role of the funding source

Novo Nordisk reviewed the article for medical accuracy only.

Conflict of interest

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